

3A (SEQ ID NO:11) from residues 1-288 or from residues 19-288, 20-288, 21-288, 22-288, 24-288, or 28-288; or as set forth in Figure 12A (SEQ ID NO: 16) from residues 1-302 or from residues 19-302, 20-302, 21-302, 22-302, 24-302 or 28-302;

Please replace the paragraph beginning at page 21, line 33, and ending at page 22, line 16, with the following:

CD28 related protein-1, or CRP1, is predicted to be a type I transmembrane protein with a signal sequence and extracellular domain at the amino-terminus, a transmembrane domain, and a carboxy terminal intracellular domain (Figure 1). The full-length CRP1 protein is 180 amino acids in its mature form. The predicted leader sequence spans about amino acid residues 1-20 (relative to the initiating methionine) and the extracellular domain of the mature protein encompasses about residues 21-145 (Example 1). The predicted transmembrane domain spans about residues 146-163 and the intracellular domain encompasses about residues 164-200. The amino terminal extracellular domain is similar to an Ig loop with conserved putative intra- and inter-molecular bonding cysteines. Furthermore, a "MYPPPY" motif (SEQ ID NO: 36), which is previously known to be important for B7.1 and B7.2 binding to CD28 and CTLA-4, is also partially conserved.

Please replace the paragraph beginning at page 22, line 29, and ending at page 23, line 7, with the following:

Human CRP1 is a transmembrane protein having the nucleotide and amino acid sequence as shown in Figure 13A (SEQ ID NOs: 21 and 22, respectively). The

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predicted leader sequence spans about residues 1-19 or about residues 1-20. The predicted mature amino terminus is at residues 20 or 21. Preferably, the mature amino terminus is at position 21. The extracellular domain spans from any of the predicted mature amino termini to about amino acid residue 140, the transmembrane domain spans about residues 141-161 and the intracellular domain spans about residues 162-199. Human CRP1 protein has 69% identity to the murine protein and the corresponding nucleotide sequences are 77% identical. The sequence of human CRP1 was reported in Hutloff et al. Nature 397, 263-266 (1999).

C. J. Jones

Please replace the paragraph beginning at page 41, line 30, and ending at page 42, line 6, with the following:

The term "CRP1 or B7RP1 polypeptide" refers to a polypeptide having the amino acid sequence of Figure 1A (SEQ ID NO:2), Figure 2A (SEQ ID NO:7) or Figure 3A (SEQ ID NO:12), or FIGURE 12A (SEQ ID NO: 17), OR FIGURE 13A (SEQ ID NO: 22) and all related polypeptides described herein. Related polypeptides includes allelic variants, splice variants, fragments, derivatives, substitution, deletion, and insertion variants, fusion polypeptides, and orthologs. Such related polypeptides may be mature polypeptides, *i.e.*, polypeptide lacking a signal peptide. A CRP1 or B7RP1 polypeptide may or may not have amino terminal methionine, depending on the manner in which they are prepared.

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Please replace the paragraph beginning at page 42, line 7, and ending at page 42, line 24, with the following:

CS
B7RP1

The term "CRP1 or B7RP1 polypeptide fragment" refers to a peptide or polypeptide that is less than the full length amino acid sequence of a CRP1 or B7RP1 polypeptide as set forth in Figure 1A (SEQ ID NO:2), Figure 2A (SEQ ID NO:7) or Figure 3A (SEQ ID NO:12), or FIGURE 12A (SEQ ID NO: 17), OR FIGURE 13A (SEQ ID NO: 22). Such a fragment may result from truncation at the amino terminus, truncation at the carboxy terminus, and/or a deletion internal to the polypeptide sequence. Such CRP1 or B7RP1 polypeptides fragments may be prepared with or without an amino terminal methionine. In addition, CRP1 or B7RP1 polypeptides fragments may be naturally-occurring splice variants, other splice variants, and fragments resulting from naturally occurring *in vivo* protease activity. Preferred CRP1 or B7RP1 polypeptide fragments include soluble forms of CRP1 or B7RP1 which lack a functional transmembrane domain and comprise part or all of the extracellular domain of either CRP1 or B7RP1.

Please replace the paragraph beginning at page 42, line 25, and ending at page 42, line 36, with the following:

C6

The term "CRP1 or B7RP1 polypeptide variants" refers to CRP1 or B7RP1 polypeptides whose amino acid sequences contain one or more amino acid sequence substitutions, deletions, and/or additions as compared to the CRP1 or B7RP1 polypeptides amino acid sequences set forth in Figure 1A (SEQ ID NO:2), Figure 2A (SEQ ID NO:7) or Figure 3A (SEQ ID NO:12), or Figure 12A (SEQ ID NO: 17), or Figure 13A (SEQ ID NO: 22). Such CRP1 or B7RP1 polypeptides variants can be prepared from the corresponding CRP1 and B7RP1 polypeptides nucleic acid molecule variants,

C-6
Conce

which have a DNA sequence that varies accordingly from the DNA sequences for CRP1 or B7RP1 polypeptides.

Please replace the paragraph beginning at page 97, line 19, and ending at page 98, line 5, with the following:

29

A cDNA clone containing an open reading frame of 199 amino acids was obtained (Figure 13A). This cDNA clone contained nucleotide and amino acid homologies to the murine CRP1 clone described in Example 1 and Figure 1. The nucleotides corresponding to the open reading frame of this human clone was 77% identical to the murine CRP1 gene. Translation of the human sequence and subsequent comparison with the murine CRP1 protein revealed 69% amino acid identity with the murine protein (Figure 13B). In addition, the motif between amino acids 114 to 119, "FDPPPF" (SEQ ID NO: 37), was conserved between the murine and human CRP1 genes. This motif corresponds to the "MYPPPY" (SEQ ID NO: 36) motif in murine and human CD28 that is essential for B7 protein interaction. Furthermore, the cysteines at amino acid positions 42, 109, and 141 are also conserved. These cysteines correspond to cysteines in CD28 and CTLA-4 that are involved in Ig loop formation and intermolecular disulfide dimerization. The close similarity with murine CRP1, and structural similarities with the CD28 homology family, indicate that this is the human CRP1 homolog.

Please replace the paragraph beginning at page 111, line 13, and ending at page 112, line 6, with the following:

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C8

The CRP1 gene in mice was disrupted by deleting a genomic fragment corresponding to nucleotides 318-591 of the murine CRP1 cDNA sequence (see SEQ ID NO:1). The murine CRP1 gene was isolated from a 129J library using the full-length (800 bp) cDNA probe (Yoshinaga et al. Nature 402, 827-832 (1999)). The targeting vector, which replaced a 2.8kb genomic fragment with a neomycin resistance (neo) cassette in sense orientation relative to CRP1 transcription, was electroporated into E14 embryonic stem (ES) cells (129/Ola, available from the American Type Culture Collection, Manassas, Va under accession no. CRL-1821). After G418 selection, homologous recombinants were identified by PCR using the primer pair GAG ACT CAT GCT GTG GTT TCA GG (SEQ ID NO: 38) and TTC GCC AAT GAC AAG ACG CTG G (SEQ ID NO: 39) and verified by Southern blotting. Chimeric mice generated from CRP1^{+/-} ES clones were crossed with C57BL6 females to produce CRP1^{+/-} mice. Germline transmission of the CRP1 mutation was assessed by PCR and Southern blot analysis of tail DNA. CRP1^{-/-} mice generated by the intercrossing of heterozygous offspring were born at the expected Mendelian frequency and were viable, fertile and of normal size. To verify that the CRP1 mutation had abolished CRP1 expression, activated T-cells from CRP1^{-/-} mice and control littermates were analyzed by flow cytometry. Upon in vitro T-cell activation, CRP1 was expressed on the surface of both CD4⁺ and CD8⁺ wild type T-cells, but was undetectable on CRP1^{-/-} T-cells.

✓
Please replace the Sequence Listing beginning after the specification at page 115, line 16, before the claims, with the enclosed Sequence Listing.

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